
A Safeguard System for Induced Pluripotent Stem Cell-Derived Rejuvenated T Cell Therapy.

Journal: Stem Cell Reports

Publication Year: 2015

Authors: Miki Ando, Toshinobu Nishimura, Satoshi Yamazaki, Tomoyuki Yamaguchi, Ai Kawana-Tachikawa, Tomonari Hayama, Yusuke Nakauchi, Jun Ando, Yasunori Ota, Satoshi Takahashi, Ken Nishimura, Manami Ohtaka, Mahito Nakanishi, John J Miles, Scott R Burrows, Malcolm K Brenner, Hiromitsu Nakauchi

PubMed link: 26321144

Funding Grants: Generation of functional cells and organs from iPSCs

Public Summary:

Adoptive T-cell immunotherapy is a potential therapeutic strategy for combating various types of cancer. However, highly expanded T cells have not proven particularly effective. This is in part explained by exhaustion and losses of function that occur during the ex vivo expansion of T cells. For an effective adoptive immunotherapy, what we need is not the "exhausted" T cells, but large numbers of "young and active" T cells that can kill tumors. To address this issue, we have recently developed a novel system in which antigen-specific killer T cells (CTLs) can be rejuvenated by reprogramming them to induced pluripotent stem cells (iPSCs) and redifferentiating them while expanding their numbers, yielding abundant rejuvenated T cells (rejT cells). We confirmed the in vivo efficacy of these rejT cell against EBV-induced tumors inoculated in immunodeficient mice. To increase the safety of this novel rejT cell therapy, we inserted a drug inducible suicide system to T cell-derived iPSCs. Both the iPSCs and rejT cells derived from them induced cell death after administration of the inducing drug in vivo thereby demonstrating efficacy of this safety system. The results facilitate clinical application of the rejT cell therapy and other branches of iPSC-derived regenerative medicine.

Scientific Abstract:

The discovery of induced pluripotent stem cells (iPSCs) has created promising new avenues for therapies in regenerative medicine. However, the tumorigenic potential of undifferentiated iPSCs is a major safety concern for clinical translation. To address this issue, we demonstrated the efficacy of suicide gene therapy by introducing inducible caspase-9 (iC9) into iPSCs. Activation of iC9 with a specific chemical inducer of dimerization (CID) initiates a caspase cascade that eliminates iPSCs and tumors originated from iPSCs. We introduced this iC9/CID safeguard system into a previously reported iPSC-derived, rejuvenated cytotoxic T lymphocyte (rejCTL) therapy model and confirmed that we can generate rejCTLs from iPSCs expressing high levels of iC9 without disturbing antigen-specific killing activity. iC9-expressing rejCTLs exert antitumor effects in vivo. The system efficiently and safely induces apoptosis in these rejCTLs. These results unite to suggest that the iC9/CID safeguard system is a promising tool for future iPSC-mediated approaches to clinical therapy.

Source URL: <https://www.cirm.ca.gov/about-cirm/publications/safeguard-system-induced-pluripotent-stem-cell-derived-rejuvenated-t-cell>